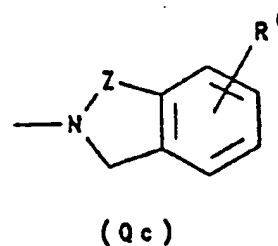
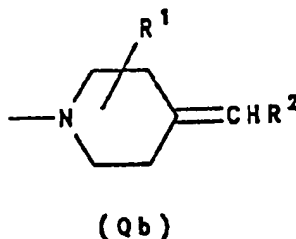
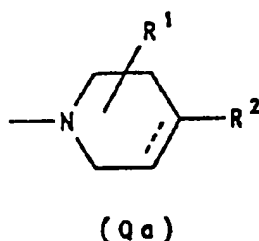
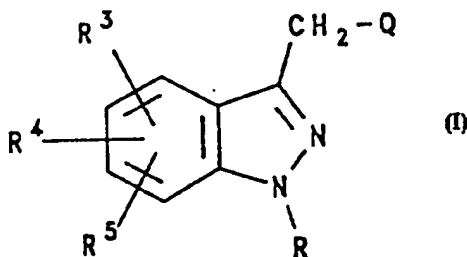




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(21) International Application Number: PCT/GB94/00503 (22) International Filing Date: 14 March 1994 (14.03.94) (30) Priority Data: 9305641.4 18 March 1993 (18.03.93) GB (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BAKER, Raymond [GB/GB]; Terlings Park, Eastwick Road, Harlows, Essex CM20 2QR (GB). KULAGOWSKI, Janusz, Jozef [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). LEESON, Paul, David [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). SMITH, Adrian, Leonard [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (74) Agent: THOMPSON, John; Merck & Co., Inc., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).	(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  Published With international search report.	

(54) Title: INDAZOLE DERIVATIVES



## (57) Abstract

A class of chemical compounds comprising a 1H-indazole moiety and a substituted heterocyclic moiety, linked via the 3-position of the indazole moiety by a methylene group, are ligands for dopamine receptor subtypes within the body and are therefore useful in the treatment and/or prevention of disorders of the dopamine system, in particular schizophrenia. In said formula (I) R represents hydrogen or C<sub>1-6</sub> alkyl, Q represents a moiety of formula Qa, Qb or Qc.

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INDAZOLE DERIVATIVES

5 This invention relates to a particular class of  
heteroaromatic compounds. More particularly, the  
invention is concerned with substituted indazole  
derivatives which are ligands for dopamine receptor  
subtypes within the body and are therefore of use in the  
treatment and/or prevention of disorders of the dopamine  
10 system, including schizophrenia, depression, nausea,  
Parkinson's disease, tardive dyskinesias and  
extrapyramidal side-effects associated with treatment by  
conventional neuroleptic agents, neuroleptic malignant  
syndrome, and disorders of hypothalamic-pituitary  
15 function such as hyperprolactinaemia and amenorrhoea.

Upper gastrointestinal tract motility is  
believed to be under the control of the dopamine system.  
The compounds according to the present invention may thus  
be of use in the prevention and/or treatment of  
20 gastrointestinal disorders, and the facilitation of  
gastric emptying.

Dependence-inducing agents such as cocaine and  
amphetamine have been shown to interact with the dopamine  
system. Compounds capable of counteracting this effect,  
25 including the compounds in accordance with the present  
invention, may accordingly be of value in the prevention  
or reduction of dependence on a dependence-inducing  
agent.

Dopamine is known to be a peripheral  
30 vasodilator; for example, it has been shown to exert a  
dilatory effect on the renal vascular bed. This implies  
that the compounds of the present invention may be  
beneficial in controlling vascular blood flow.

The localisation of dopamine receptor mRNA in  
35 rat heart and large vessels has been noted. This  
suggests a role for dopamine receptor ligands in

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controlling cardiovascular function, either by affecting cardiac and smooth muscle contractility or by modulating the secretion of vasoactive substances. The compounds according to the present invention may therefore be of assistance in the prevention and/or treatment of such conditions as hypertension and congestive heart failure.

Molecular biological techniques have revealed the existence of several subtypes of the dopamine receptor. The dopamine D<sub>1</sub> receptor subtype has been shown to occur in at least two discrete forms. Two forms of the D<sub>2</sub> receptor subtype, and at least one form of the D<sub>3</sub> receptor subtype, have also been discovered. More recently, the D<sub>4</sub> (Van Tol et al., Nature (London), 1991, 350, 610) and D<sub>5</sub> (Sunahara et al., Nature (London), 1991, 350, 614) receptor subtypes have been described.

The disclosure of US-3678059 generically encompasses inter alia a class of 3-[piperidin-1-ylalkyl]indazole derivatives substituted on the indazole nitrogen atom by an araliphatic or aromatic radical. These compounds are alleged therein to possess antidepressant and anti-inflammatory activity. There is, however, no suggestion in US-3678059 that such compounds would be of benefit in the treatment and/or prevention of disorders of the dopamine system.

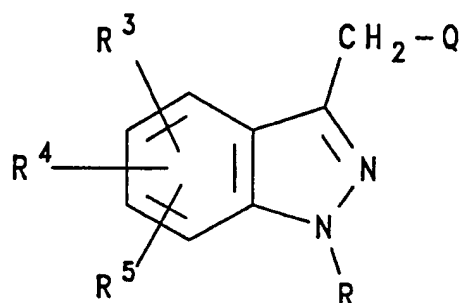
The generic disclosure of EP-A-0449186 encompasses inter alia a series of substituted piperidin-1-ylalkyl-indazole derivatives which are stated to be antipsychotic agents that act by selective antagonism of the sigma receptor. There is, however, no specific disclosure therein of a [4-substituted-piperidin-1-ylmethyl]-1H-indazole derivative. Moreover, there is no suggestion in EP-A-0449186 that the compounds described therein would be of benefit in the treatment and/or prevention of disorders of the dopamine system. Indeed, it is explicitly stated in EP-A-0449186 that the compounds described therein do not bind to the dopamine

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receptors or only have weak binding for the dopamine receptors.

The compounds in accordance with the present invention, being ligands for dopamine receptor subtypes within the body, are accordingly of use in the treatment and/or prevention of disorders of the dopamine system.

The present invention accordingly provides a compound of formula I, or a salt or prodrug thereof:



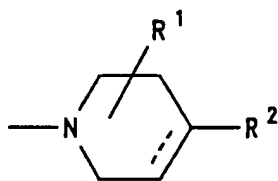
( I )

wherein

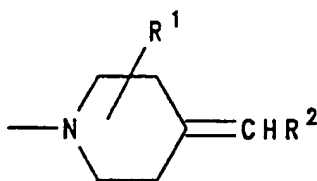
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R represents hydrogen or C<sub>1-6</sub> alkyl;

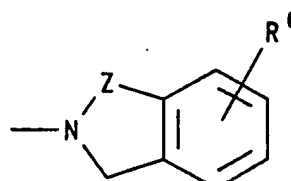
Q represents a moiety of formula Qa, Qb or Qc:



( Q a )



( Q b )



( Q c )

30 in which the broken line represents an optional chemical bond;

R<sup>1</sup> represents hydrogen, or an optionally substituted C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl(C<sub>1-6</sub>)alkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, aryl(C<sub>1-6</sub>)alkoxy, 35 aryl(C<sub>2-6</sub>)alkenyl, aryl(C<sub>2-6</sub>)alkynyl, heteroaryl,

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heteroaryl(C<sub>1-6</sub>)alkyl, heteroaryl(C<sub>2-6</sub>)alkenyl or heteroaryl(C<sub>2-6</sub>)alkynyl group;

R<sup>2</sup> represents an optionally substituted C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl(C<sub>1-6</sub>)alkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, aryl(C<sub>1-6</sub>)alkoxy, aryl(C<sub>2-6</sub>)alkenyl, aryl(C<sub>2-6</sub>)alkynyl, heteroaryl, heteroaryl(C<sub>1-6</sub>)alkyl, heteroaryl(C<sub>2-6</sub>)alkenyl or heteroaryl(C<sub>2-6</sub>)alkynyl group;

R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, -OR<sup>a</sup>, -SR<sup>a</sup>, -SOR<sup>a</sup>, -SO<sub>2</sub>R<sup>a</sup>, -SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>COR<sup>b</sup>, -NR<sup>a</sup>CO<sub>2</sub>R<sup>b</sup>, -COR<sup>a</sup>, -CO<sub>2</sub>R<sup>a</sup> or -CONR<sup>a</sup>R<sup>b</sup>;

Z represents -CH<sub>2</sub>- or -CH<sub>2</sub>CH<sub>2</sub>-;

R<sup>6</sup> represents hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, aryl(C<sub>1-6</sub>)alkyl or halogen; and

R<sup>a</sup> and R<sup>b</sup> independently represent hydrogen, hydrocarbon or a heterocyclic group.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g.

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calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing  
5 up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl(C<sub>1-6</sub>)alkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, aryl(C<sub>2-6</sub>)alkenyl and  
10 aryl(C<sub>2-6</sub>)alkynyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic  
15 group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C<sub>3-7</sub> heterocycloalkyl, C<sub>3-7</sub> heterocycloalkyl(C<sub>1-6</sub>)alkyl, heteroaryl, heteroaryl(C<sub>1-6</sub>)alkyl, heteroaryl(C<sub>2-6</sub>)alkenyl and  
20 heteroaryl(C<sub>2-6</sub>)alkynyl groups.

Suitable alkyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R, R<sup>1</sup>, R<sup>2</sup> and R<sup>6</sup> include straight-  
25 chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl.

Suitable alkenyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R<sup>1</sup> and R<sup>2</sup> include straight-chained and  
30 branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.

Suitable alkynyl groups within the scope of the term "hydrocarbon" and within the definition of the  
35

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substituents  $R^1$  and  $R^2$  include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

5           Suitable cycloalkyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents  $R^1$  and  $R^2$  include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

10           Particular cycloalkyl( $C_{1-6}$ )alkyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents  $R^1$  and  $R^2$  include cyclopropylmethyl, cyclohexylmethyl and cyclohexylethyl.

15           Particular aryl groups within the scope of the term "hydrocarbon" and within the definition of the substituents  $R^1$  and  $R^2$  include phenyl and naphthyl.

20           Particular aryl( $C_{1-6}$ )alkyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents  $R^1$ ,  $R^2$  and  $R^6$  include benzyl, naphthylmethyl, phenethyl and phenylpropyl.

A particular aryl( $C_{2-6}$ )alkenyl group within the scope of the term "hydrocarbon" and within the definition of the substituents  $R^1$  and  $R^2$  is phenylethenyl.

25           A particular aryl( $C_{2-6}$ )alkynyl group within the scope of the term "hydrocarbon" and within the definition of the substituents  $R^1$  and  $R^2$  is phenylethynyl.

Suitable heterocycloalkyl groups include azetidiny, pyrrolidyl, piperidyl, piperazinyl and morpholinyl groups.

30           Suitable heteroaryl groups within the scope of the expression "a heterocyclic group" and within the definition of the substituents  $R^1$  and  $R^2$  include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, 35   thienyl, benzthienyl, indolyl, indazolyl, imidazolyl, benzimidazolyl, oxadiazolyl and thiadiazolyl groups.



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Particular heteroaryl(C<sub>1-6</sub>)alkyl groups within the scope of the expression "a heterocyclic group" and within the definition of the substituents R<sup>1</sup> and R<sup>2</sup> include thienylmethyl, pyridylmethyl, pyrimidinylmethyl and pyrazinylmethyl.

The hydrocarbon and heterocyclic groups, as well as the substituents R<sup>1</sup> and R<sup>2</sup>, may in turn be optionally substituted by one or more groups selected from C<sub>1-6</sub> alkyl, adamantyl, phenyl, aryl(C<sub>1-6</sub>)alkyl, halogen, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> aminoalkyl, trifluoromethyl, hydroxy, C<sub>1-6</sub> alkoxy, aryloxy, keto, C<sub>1-3</sub> alkylenedioxy, nitro, cyano, carboxy, C<sub>2-6</sub> alkoxycarbonyl, C<sub>2-6</sub> alkoxycarbonyl(C<sub>1-6</sub>)alkyl, C<sub>2-6</sub> alkylcarbonyloxy, arylcarbonyloxy, C<sub>2-6</sub> alkylcarbonyl, arylcarbonyl, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulphinyl, C<sub>1-6</sub> alkylsulphonyl, arylsulphonyl, -NR<sup>V</sup>R<sup>W</sup>, -NR<sup>V</sup>COR<sup>W</sup>, -NR<sup>V</sup>CO<sub>2</sub>R<sup>W</sup>, -NR<sup>V</sup>SO<sub>2</sub>R<sup>W</sup>, -CH<sub>2</sub>NR<sup>V</sup>SO<sub>2</sub>R<sup>W</sup>, -NHCONR<sup>V</sup>R<sup>W</sup>, -CONR<sup>V</sup>R<sup>W</sup>, -SO<sub>2</sub>NR<sup>V</sup>R<sup>W</sup> and -CH<sub>2</sub>SO<sub>2</sub>NR<sup>V</sup>R<sup>W</sup>, in which R<sup>V</sup> and R<sup>W</sup> independently represent hydrogen, C<sub>1-6</sub> alkyl, aryl or aryl(C<sub>1-6</sub>)alkyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially chlorine.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres,

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they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

5                   Suitably, the substituent R represents hydrogen or methyl, especially hydrogen.

                  Suitably, the substituent R<sup>1</sup> represents hydrogen or methyl, especially hydrogen.

                  Suitable values for the substituent R<sup>2</sup> include  
10   C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl(C<sub>1-6</sub>)alkyl, aryl,  
     aryl(C<sub>1-6</sub>)alkyl, aryl(C<sub>2-6</sub>)alkenyl and heteroaryl, any of  
     which groups may be optionally substituted. Examples of  
     optional substituents on the group R<sup>2</sup> include C<sub>1-6</sub> alkyl,  
     halogen, trifluoromethyl, C<sub>1-6</sub> alkoxy, C<sub>1-3</sub>  
15   alkylenedioxy, nitro and C<sub>2-6</sub> alkylcarbonyl.

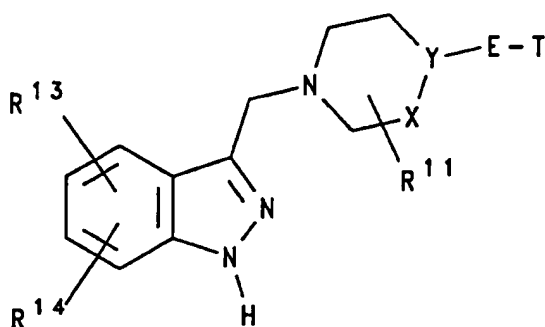
                  Particular values of R<sup>2</sup> include methyl, ethyl,  
     n-propyl, isopropyl, cyclohexyl-ethyl, phenyl,  
     methylphenyl, ethylphenyl, fluorophenyl, chlorophenyl,  
     trifluoromethyl-phenyl, methoxyphenyl, methylenedioxy-  
20   phenyl, acetylphenyl, nitrophenyl, naphthyl, benzyl,  
     chlorobenzyl, methylenedioxy-benzyl, phenethyl,  
     phenylethenyl, benzofuryl, indolyl, pyridyl,  
     chloropyridyl, methylpyridyl, methoxypyridyl, quinolyl,  
     isoquinolyl and pyrimidinyl.

25                   Suitable values for the substituents R<sup>3</sup>, R<sup>4</sup> and  
     R<sup>5</sup> include hydrogen, halogen, cyano, nitro,  
     trifluoromethyl, amino, C<sub>1-6</sub> alkylamino,  
     di(C<sub>1-6</sub>)alkylamino, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy,  
     aryl(C<sub>1-6</sub>)alkoxy and C<sub>2-6</sub> alkylcarbonyl. Particular  
30   values include hydrogen, fluoro, chloro, methyl, methoxy  
     and benzyloxy.

                  Particular values of R<sup>6</sup> include hydrogen,  
     chloro and bromo.

35                   One sub-class of compounds according to the  
     invention is represented by the compounds of formula IIA,  
     and salts and prodrugs thereof:

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(IIA)

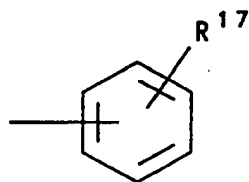
wherein

E represents  $-(CH_2)_n-$ ,  $-CH=CH-$  or  $-C\equiv C-$ ;

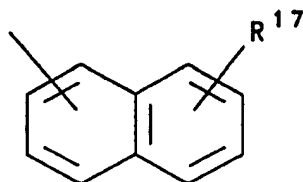
n is zero, 1, 2 or 3;

$-X-Y-$  represents  $-CH_2-CH-$  or  $-CH=C-$ ;

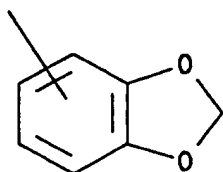
15 T represents a group of formula (i), (ii),  
(iii) or (iv):



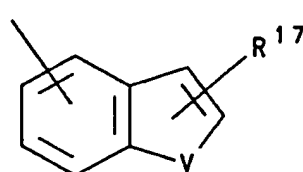
(i)



(ii)



(iii)



(iv)

in which V represents oxygen, sulphur or NH;

$R^{11}$  represents hydrogen or  $C_{1-6}$  alkyl; and

35  $R^{13}$ ,  $R^{14}$  and  $R^{17}$  independently represent  
hydrogen, halogen, cyano, nitro, trifluoromethyl, amino,

- 10 -

C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub>)alkylamino, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, aryl(C<sub>1-6</sub>)alkoxy or C<sub>2-6</sub> alkylcarbonyl.

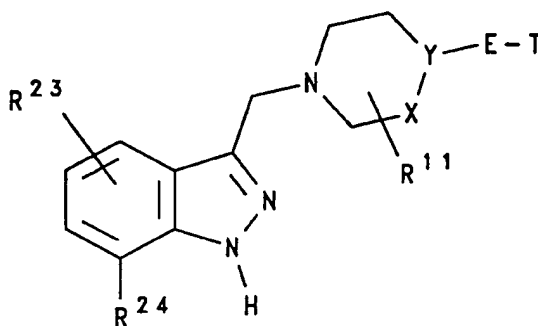
Particular values of R<sup>11</sup> include hydrogen and methyl, especially hydrogen.

5 Particular values of R<sup>13</sup> and R<sup>14</sup> include hydrogen, halogen, methyl, ethyl, methoxy and benzyloxy, especially hydrogen, fluoro and chloro. Suitably, one of R<sup>13</sup> and/or R<sup>14</sup> is hydrogen.

10 Particular values of R<sup>17</sup> include hydrogen, fluoro, chloro, trifluoromethyl, methyl, methoxy, acetyl and nitro.

A particular subset of the compounds of formula IIA as defined above is represented by the compounds of formula IIB, and salts and prodrugs thereof:

15



(IIB)

25 wherein

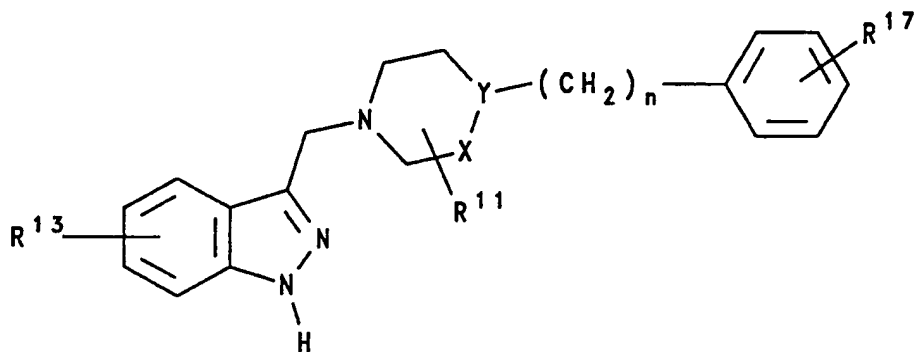
X, Y, R<sup>11</sup>, E and T are as defined with reference to formula IIA above; and

R<sup>23</sup> and R<sup>24</sup> independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub>)alkylamino, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, aryl(C<sub>1-6</sub>)alkoxy or C<sub>2-6</sub> alkylcarbonyl.

30 Particular values of R<sup>23</sup> and R<sup>24</sup> include hydrogen, halogen, methyl, ethyl, methoxy and benzyloxy, especially hydrogen, fluoro and chloro. Suitably, R<sup>24</sup> is  
35 hydrogen, fluoro or chloro.

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Another subset of the compounds of formula IIA as defined above is represented by the compounds of formula IIC, and salts and prodrugs thereof:

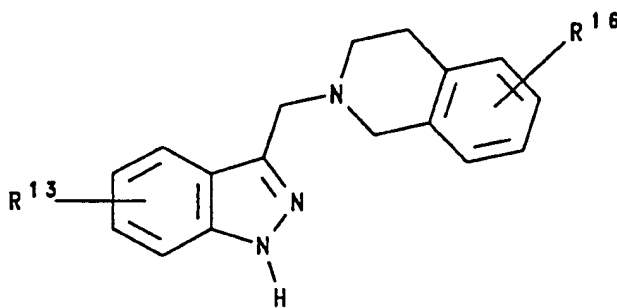


(IIC)

15 wherein  $n$ ,  $X$ ,  $Y$ ,  $R^{11}$ ,  $R^{13}$  and  $R^{17}$  are as defined with reference to formula IIA above.

A further sub-class of compounds according to the invention is represented by the compounds of formula IID, and salts and prodrugs thereof:

20



(IID)

30 wherein

$R^{13}$  is as defined with reference to formula IIA above; and

$R^{16}$  represents hydrogen,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, aryl( $C_{1-6}$ )alkyl or halogen.

35 Particular values of  $R^{16}$  include hydrogen, chloro and bromo, especially hydrogen.

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Specific compounds within the scope of the present invention include:

- 3-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-1H-indazole;  
3-[4-(2-phenylethyl)piperidin-1-ylmethyl]-1H-indazole;  
5 3-[4-(2-cyclohexylethyl)piperidin-1-ylmethyl]-1H-indazole;  
6-fluoro-3-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-1H-indazole;  
7-chloro-3-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-1H-indazole;  
10 6-chloro-3-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-1H-indazole;  
7-chloro-3-[4-(2-phenylethyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
15 (E)-3-[4-(2-phenylethenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
7-chloro-(E)-3-[4-(2-phenylethenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
3-[4-(naphthalen-2-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
20 7-chloro-3-[4-(4-chlorophenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
3-[4-(4-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
25 7-chloro-3-[4-(4-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
7-fluoro-3-[4-(4-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
6,7-difluoro-3-[4-(4-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
30 3-[4-(benzofuran-5-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
3-[4-(benzofuran-5-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-7-chloro-1H-indazole;  
35 3-[4-(benzo[1,3]dioxolan-5-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;

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3-[4-(1H-indol-5-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-  
1H-indazole;

7-chloro-3-[4-(1H-indol-5-yl)-3,6-dihydro-2H-pyridin-1-  
ylmethyl]-1H-indazole;

5 and salts and prodrugs thereof.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in  
10 unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal  
15 administration, or for administration by inhalation or insufflation. Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be  
20 adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose,  
25 sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these  
30 preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such  
35 as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit

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dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

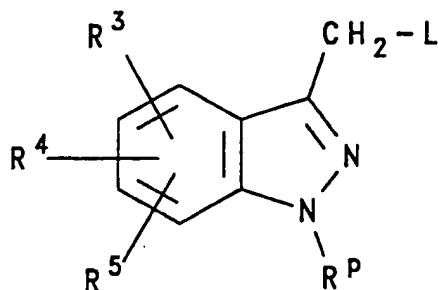
In the treatment of schizophrenia, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds in accordance with the present invention may be prepared by a process which comprises

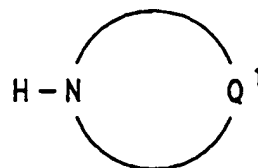


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reacting a compound of formula III with a compound of formula IV:



(III)



(IV)

wherein  $R^3$ ,  $R^4$  and  $R^5$  are as defined above,  $Q^1$  represents  
 15 the residue of a moiety of formula Qa to Qc as defined  
 above, L represents a suitable leaving group, and  $R^P$   
 corresponds to the group R as defined above or represents  
 a suitable protecting group; followed, where required, by  
 removal of the protecting group  $R^P$ ; and subsequently, if  
 20 necessary, N-alkylation by standard methods to introduce  
 the moiety R.

The leaving group L is suitably a halogen atom,  
 e.g. bromine.

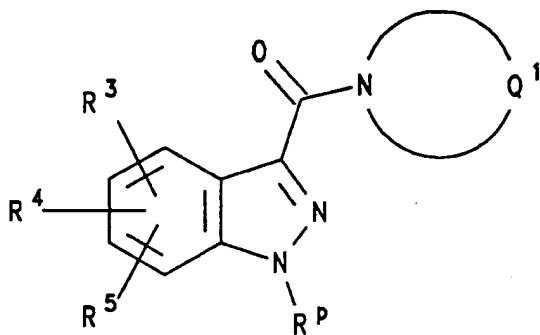
The protecting group  $R^P$  on the indazole  
 25 nitrogen atom, when present, is suitably an acyl moiety  
 such as acetyl, which can conveniently be removed as  
 necessary by treatment under strongly basic conditions,  
 e.g. sodium methoxide in methanol. Alternatively, the  
 protecting group  $R^P$  may be a carbamoyl moiety such as  
 30 t-butoxycarbonyl (BOC), which can conveniently be removed  
 as necessary by treatment under mildly acidic conditions.

The reaction between compounds III and IV is  
 conveniently carried out by stirring the reactants under  
 basic conditions in a suitable solvent, for example  
 35 potassium carbonate in N,N-dimethylformamide;

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triethylamine in tetrahydrofuran or acetonitrile; or diisopropylethylamine (Hünig's base) in dichloromethane.

In an alternative procedure, the compounds in accordance with the present invention may be prepared by a process which comprises reducing a compound of formula V:

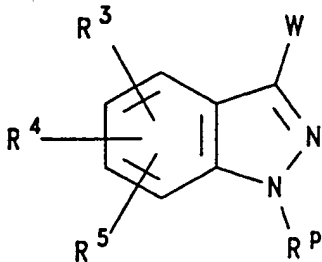


(V)

wherein  $Q^1$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $R^P$  are as defined above; followed, where required, by removal of the protecting group  $R^P$ ; and subsequently, if necessary, N-alkylation by standard methods to introduce the moiety R.

The reaction is conveniently carried out by treating the compound V with a reducing agent such as lithium aluminium hydride in an appropriate solvent, e.g. tetrahydrofuran.

The intermediates of formula V above may suitably be prepared by reacting a compound of formula IV as defined above with a compound of formula VI:



(VI)

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wherein  $R^3$ ,  $R^4$ ,  $R^5$  and  $R^D$  are as defined above; and W represents a reactive carboxylate moiety.

Suitable values for the reactive carboxylate moiety W include esters, for example  $C_{1-4}$  alkyl esters; acid anhydrides, for example mixed anhydrides with  $C_{1-4}$  alkanolic acids; acid halides, for example acid chlorides; and acylimidazoles.

By way of example, the intermediates of formula VI above wherein W is an acid chloride moiety may be prepared by treating the corresponding carboxylic acid derivative with thionyl chloride in toluene. Similarly, the intermediates of formula VI wherein W is an acylimidazole moiety may be prepared by treating the corresponding carboxylic acid derivative with 1,1'-carbonyldiimidazole. Alternatively, the reactive carboxylate moiety W may be obtained by treating the corresponding compound wherein W is carboxy with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate, optionally in the presence of triethylamine; the resulting activated carboxylate intermediate may then suitably be reacted in situ with the required compound of formula IV.

Where they are not commercially available, the starting materials of formula III, IV and VI may be prepared by procedures analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be appreciated that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further desired compound of formula I using techniques known from the art. For example, a compound of formula I wherein R is hydrogen initially obtained may be converted into a compound of formula I wherein R represents  $C_{1-6}$  alkyl by standard alkylation techniques, such as by treatment with an alkyl iodide,

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e.g. methyl iodide, typically under basic conditions,  
e.g. sodium hydride in dimethylformamide, or  
triethylamine in acetonitrile.

Where the above-described processes for the  
5 preparation of the compounds according to the invention  
give rise to mixtures of stereoisomers, these isomers may  
be separated by conventional techniques such as  
preparative chromatography. The compounds may be  
prepared in racemic form, or individual enantiomers may  
10 be prepared either by enantiospecific synthesis or by  
resolution. The compounds may, for example, be resolved  
into their component enantiomers by standard techniques  
such as preparative HPLC, or the formation of  
diastereomeric pairs by salt formation with an optically  
15 active acid, such as (-)-di-p-toluoyl-d-tartaric acid  
and/or (+)-di-p-toluoyl-l-tartaric acid, followed by  
fractional crystallization and regeneration of the free  
base. The compounds may also be resolved by formation of  
diastereomeric esters or amides, followed by  
20 chromatographic separation and removal of the chiral  
auxiliary.

During any of the above synthetic sequences it  
may be necessary and/or desirable to protect sensitive or  
reactive groups on any of the molecules concerned. This  
25 may be achieved by means of conventional protecting  
groups, such as those described in Protective Groups in  
Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973;  
and T.W. Greene & P.G.M. Wuts, Protective Groups in  
Organic Synthesis, John Wiley & Sons, 1991. The  
30 protecting groups may be removed at a convenient  
subsequent stage using methods known from the art.

The following Examples illustrate the  
preparation of compounds according to the invention.

The compounds useful in this invention potentially  
35 inhibit [<sup>3</sup>H]-spiperone binding to human dopamine D<sub>4</sub>  
receptor subtypes expressed in clonal cell lines.

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### [<sup>3</sup>H]-Spiperone Binding Studies

Clonal cell lines expressing the human dopamine D<sub>4</sub> receptor subtype were harvested in PBS and then lysed in 10 mM Tris-HCl pH 7.4 buffer containing 5 mM MgSO<sub>4</sub> for 20 min on ice. Membranes were centrifuged at 50,000g for 15 min at 4°C and the resulting pellets resuspended in assay buffer (50 mM Tris-HCl pH 7.4 containing 5 mM EDTA, 1.5 mM CaCl<sub>2</sub>, 5 mM MgCl<sub>2</sub>, 5 mM KCl, 120 mM NaCl, and 0.1% ascorbic acid) at 20 mg/ml wet weight. Incubations were carried out for 60 min at room temperature (22°C) in the presence of 0.05-2 nM [<sup>3</sup>H]-spiperone or 0.2 nM for displacement studies and were initiated by addition of 20-100 µg protein in a final assay volume of 0.5 ml. The incubation was terminated by rapid filtration over GF/B filters presoaked in 0.3% PEI and washed with 10 ml ice-cold 50 mM Tris-HCl, pH 7.4. Specific binding was determined by 10 µM apomorphine and radioactivity determined by counting in a LKB beta counter. Binding parameters were determined by non-linear least squares regression analysis, from which the inhibition constant K<sub>i</sub> could be calculated for each test compound.

The compounds of the accompanying Examples were tested in the above assay, and all were found to possess a K<sub>i</sub> value for displacement of [<sup>3</sup>H]-spiperone from the human dopamine D<sub>4</sub> receptor subtype of below 1.5 µM.

**EXAMPLES**

**General techniques:** All reactions were carried out under a nitrogen atmosphere using anhydrous solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically (HPLC / TLC) and spectroscopically (<sup>1</sup>H NMR) homogeneous materials, unless otherwise stated.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light and/or I<sub>2</sub> vapour for visualisation. Fluka silica gel (60, particle size 0.035 – 0.070 mm) was used for flash chromatography.

**EXAMPLE 1****2-(1*H*-Indazol-3-ylmethyl)-1,2,3,4-tetrahydroisoquinoline**

1*H*-Indazole-3-carboxylic acid (1.50 g, 9.25 mmol), 1,2,3,4-tetrahydroisoquinoline (1.60 g, 12 mmol), 1-hydroxybenzotriazole hydrate (1.65 g, 12 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (2.35 g, 12 mmol) were dissolved in dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>, 50 mL) and the solution was stirred at 20°C for 14 h. The solution was poured into 2 M aqueous HCl (100 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL). The combined organic extracts were washed with saturated aqueous NaHCO<sub>3</sub> (50 mL), dried (MgSO<sub>4</sub>) and concentrated to give a yellow solid (2.67 g) which was sparingly soluble in CH<sub>2</sub>Cl<sub>2</sub> or ethyl acetate (EtOAc); mp 199–200 °C (from EtOAc).

A solution of the above solid (2.67 g, 9.25 mmol) in tetrahydrofuran (THF, 25 mL) was treated with LiAlH<sub>4</sub> (24 mL

of a 1.0 M solution in THF, 24 mmol) and the resulting solution was heated at 60°C for 14 h. The solution was cooled, quenched by the cautious addition of 2M aqueous NaOH (4 mL), stirred for 1 h at 20°C, filtered washing with EtOAc, and the filtrate was concentrated and the residue purified by flash chromatography (50% EtOAc in hexane) to give the free base of the title compound as a colourless viscous oil.

The oil was dissolved in methanol (20 mL) and added to a solution of oxalic acid (1.0 g, 11 mmol) in methanol (10 mL). The solution was diluted with Et<sub>2</sub>O (400 mL) and the oxalate salt precipitated as a fine white crystalline powder which was collected by filtration, washing with Et<sub>2</sub>O; mp 151–152°C (from MeOH / Et<sub>2</sub>O); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO) δ 7.91 (d, *J* = 8.0 Hz, 1 H, aromatic), 7.54 (d, *J* = 8.4 Hz, 1 H, aromatic), 7.37 (dt, *J* = 0.8, 6.7 Hz, 1 H, aromatic), 7.17 – 7.06 (m, 5 H, aromatic), 5.0 – 4.0 (bs, 4 H, NH, (COOH)<sub>2</sub>, H<sub>2</sub>O), 4.36 (s, 2 H, CH<sub>2</sub>-N), 3.99 (s, 2 H, indazole-CH<sub>2</sub>-N), 3.11 (bs, 2 H, CH<sub>2</sub>CH<sub>2</sub>-N), 2.93 (t, *J* = 5.9 Hz, CH<sub>2</sub>CH<sub>2</sub>-N); MS (CI+) *m/e* 264 (M+H<sup>+</sup>); Anal. calcd for C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>.(COOH)<sub>2</sub>. H<sub>2</sub>O: C, 62.97; H, 5.56; N, 11.60. Found: C, 63.00; H, 5.48; N, 11.60.

## EXAMPLE 2

### 3-(4-Phenethylpiperidin-1-ylmethyl)-1H-indazole

#### Step A: 1-Acetyl-3-methyl-1H-indazole

3-Methyl-1H-indazole (6.157 g, 44.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was treated with acetic anhydride (22.75 g, 223 mmol), triethylamine (22.5 g, 223 mmol) and DMAP (0.54 g, 4.5 mmol). The mixture was stirred 1 h at 20°C, poured into water (100 mL)

and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 100 mL). The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and the residue recrystallised from hexane to give the title compound (4.12 g, 66%) as a white crystalline solid; mp 70 – 71 °C (from hexane); <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ 8.41 (d, *J* = 8.4 Hz, 1 H, indazole), 7.64 (d, *J* = 8.4 Hz, 1 H, indazole), 7.54 (t, *J* = 8.4 Hz, 1 H, indazole), 7.35 (t, *J* = 8.4 Hz, 1 H, indazole), 2.75 (s, 3 H, Ac), 2.58 (s, 3 H, Me); MS (CI+) *m/e* 175 (M+H<sup>+</sup>); Anal. calcd for C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O: C, 68.95; H, 5.97; N, 16.08. Found: C, 68.80; H, 5.58; N, 16.18.

10                    Step B: 1-Acetyl-3-bromomethyl-1*H*-indazole

1-Acetyl-3-methyl-1*H*-indazole (5.77 g, 33.1 mmol) in CCl<sub>4</sub> (150 mL) was treated with *N*-bromosuccinimide (6.49 g, 36.5 mmol) and benzoyl peroxide (0.80 g, 3.3 mmol) and the mixture was heated at 70°C for 16 h. The mixture was concentrated and the residue quickly filtered through a plug of flash silica eluting with 0 → 5% EtOAc in hexane to give the crude title compound contaminated with traces of dibromide and starting material. This was conveniently used directly in subsequent reactions without further purification.

20                    Step C: 3-(-4-Phenethylpiperidin-1-ylmethyl)-1*H*-indazole

1-Acetyl-3-bromomethyl-1*H*-indazole (0.50 g, 1.98 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was treated with 4-phenethylpiperidine hydrochloride (0.893 g, 3.96 mmol) and Hünig's base (0.78 g, 5.94 mmol) and the mixture stirred at 20°C for 16 h. The mixture was poured into saturated aqueous sodium bicarbonate solution (25 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 25 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), concentrated and the residue purified by flash chromatography (0% → 10% EtOAc in hexane) to give 1-acetyl-3-(4-phenethylpiperidin-1-ylmethyl)-1*H*-



indazole as a colourless oil (98 mg, 14%). This was dissolved in CH<sub>2</sub>Cl<sub>2</sub> / methanol (1 : 1, 10 mL), treated with NaOMe (2 mg) and stirred for 15 min at 20 °C. The mixture was poured into saturated aqueous sodium bicarbonate solution (25 mL) and  
5 extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 25 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), concentrated and the residue recrystallised from EtOAc / hexane to give the title compound (55 mg, 69%) as colourless crystals; mp 153–155°C (from EtOAc / hexane); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO) δ 12.75 (bs, 1 H, NH),  
10 7.84 (d, *J* = 8.1 Hz, 1 H, indazole), 7.46 (d, *J* = 8.4 Hz, 1 H, indazole), 7.31 (t, *J* = 6.7 Hz, 1 H, indazole), 7.27 – 7.12 (m, 5 H, Ph), 7.07 (t, *J* = 7.1 Hz, 1 H, indazole), 3.78 (s, 2 H, Ar-CH<sub>2</sub>N), 2.85 (m, 2 H, aliphatic), 2.56 (m, 2 H, aliphatic), 1.94 (m, 2 H, aliphatic), 1.65 (m, 2 H, aliphatic), 1.47 (m, 2 H, aliphatic), 1.16  
15 (m, 3 H, aliphatic); MS (CI+) *m/e* 320 (M+H<sup>+</sup>); Anal. calcd for C<sub>21</sub>H<sub>25</sub>N<sub>3</sub>: C, 78.96; H, 7.89; N, 13.15. Found: C, 78.94; H, 7.96; N, 12.89.

### EXAMPLE 3

#### 3-[4-(2-Cyclohexylethyl)piperidin-1-ylmethyl]-1H-indazole

20 The title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 2; mp 145–146°C (from EtOAc); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO) δ 12.75 (bs, 1 H, NH), 7.83 (d, *J* = 8.1 Hz, 1 H, indazole), 7.46 (d, *J* = 8.4 Hz, 1 H, indazole), 7.31 (t, *J* = 6.7 Hz, 1 H, indazole), 7.07  
25 (t, *J* = 7.1 Hz, 1 H, indazole), 3.78 (s, 2 H, Ar-CH<sub>2</sub>N), 2.83 (m, 2 H, aliphatic), 1.93 (m, 2 H, aliphatic), 1.63 (m, 7 H, aliphatic), 1.14 (m, 11 H, aliphatic), 0.85 (m, 2 H, aliphatic); MS (CI+) *m/e* 326 (M+H<sup>+</sup>); Anal. calcd for C<sub>21</sub>H<sub>31</sub>N<sub>3</sub>: C, 77.49; H, 9.60; N, 12.91. Found: C, 77.38; H, 9.59; N, 12.72.

EXAMPLE 42-(6-Fluoro-1*H*-indazol-3-ylmethyl)-1,2,3,4-tetrahydroisoquinolineStep A: 1-(2-Amino-4-fluorophenyl)ethanone

5           A solution of BCl<sub>3</sub> (110 mL of a 1.0 M solution in CH<sub>2</sub>Cl<sub>2</sub>, 110 mmol) was cooled to 0°C and treated with a solution of 3-fluoroaniline (10 mL, 104 mmol) in 1,1,2,2-tetrachloroethane (200 mL). The resulting solution was stirred 15 min and treated with MeCN (16.3 mL, 330 mmol) and AlCl<sub>3</sub> (14.7 g, 110 mmol) and heated at 120°C for 16 h with distillative removal of CH<sub>2</sub>Cl<sub>2</sub>. The mixture was cooled to 0°C and quenched with 2 M aqueous HCl (250 mL). The mixture was heated at 80 °C for 1 h to hydrolyse the imine, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 x 100 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), concentrated and purified by flash chromatography (10% EtOAc in hexane) to give the title compound (9.618 g, 60%) as a low melting pale yellow crystalline solid; <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO) δ 7.81 (dd, *J* = 8.9, 6.7 Hz, 1 H, Ph), 7.43 (bs, 2 H, NH<sub>2</sub>), 6.49 (dd, *J* = 12.0, 2.6 Hz, 1 H, Ph), 6.35 (dt, *J* = 8.9, 0.7 Hz, 1 H, Ph), 2.48 (s, 3 H, Me).

Step B: 6-Fluoro-3-methyl-1*H*-indazole

1-(2-Amino-4-fluorophenyl)ethanone (9.618 g, 62.9 mmol) was treated with concentrated hydrochloric acid (16 mL) and water (16 mL), and the resulting white suspension was cooled to -10°C and treated with a solution of sodium nitrite (4.338 g, 62.9 mmol) in 10 mL H<sub>2</sub>O, maintaining the temperature below 0°C. The resulting solution was filtered directly into a rapidly stirred solution of SnCl<sub>2</sub>·2H<sub>2</sub>O (34 g in 200 mL H<sub>2</sub>O) and the resulting

mixture was stirred for 1 h at 20°C, basified (32 g NaOH in 200 mL H<sub>2</sub>O) and extracted with EtOAc. The combined organic extracts were dried (MgSO<sub>4</sub>), concentrated and the residue purified by flash chromatography (25% EtOAc in hexane) to give the title compound (3.10 g, 33%) as a white solid; mp 116–117°C (from hexane); <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ 12.89 (bs, 1 H, NH), 7.62 (dd, *J* = 8.8, 5.1 Hz, 1 H, indazole), 7.09 (dd, *J* = 9.1, 2.0 Hz, 1 H, indazole), 6.93 (dt, *J* = 9.1, 2.0 Hz, 1 H, indazole), 2.60 (s, 3 H, Me); MS (CI+) *m/e* 151 (M+H<sup>+</sup>); Anal. calcd for C<sub>8</sub>H<sub>7</sub>FN<sub>2</sub>: C, 63.99, H, 4.70; N, 18.66. Found: C, 63.94; H, 4.72; N, 19.10.

Step C: 1-Acetyl-6-fluoro-3-methyl-1*H*-indazole

6-Fluoro-3-methyl-1*H*-indazole (2.79 g, 18.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was treated with acetic anhydride (2.8 g, 30 mmol), Hünig's base (5.2 mL, 30 mmol) and DMAP (0.2 g, 1.7 mmol). The mixture was stirred 1 h at 20°C, poured into water (100 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 100 mL). The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and the residue recrystallised from hexane to give the title compound (3.41 g, 96%) as a white crystalline solid; mp 89–91°C (from hexane); <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ 8.05 (dd, *J* = 9.4, 2.2 Hz, 1 H, indazole), 7.51 (dd, *J* = 8.7, 5.1 Hz, 1 H, indazole), 7.03 (dt, *J* = 8.8, 2.2 Hz, 1 H, indazole), 2.67 (s, 3 H, Me), 2.49 (s, 3 H, Ac); MS (CI+) *m/e* 193 (M+H<sup>+</sup>); Anal. calcd for C<sub>10</sub>H<sub>9</sub>FN<sub>2</sub>O: C, 62.49; H, 4.72; N, 14.58. Found: C, 62.50; H, 4.79; N, 14.63.

Step D: 1-Acetyl-3-bromomethyl-6-fluoro-1*H*-indazole

1-Acetyl-6-fluoro-3-methyl-1*H*-indazole (5.77 g, 33.1 mmol) in CCl<sub>4</sub> (100 mL) was treated with NBS (3.64 g, 20 mmol) and benzoyl peroxide (0.388 g, 1.6 mmol) and the mixture was heated at 70°C for 6 h. The mixture was concentrated and the

residue quickly filtered through a plug of flash silica eluting with 2% → 7% EtOAc in hexane to give the crude title compound (2.97 g, 65%) contaminated with traces of dibromide and starting material. This was conveniently used directly in subsequent reactions without further purification.

1-Acetyl-3-bromomethyl-6-chloro-1*H*-indazole, 1-acetyl-3-bromomethyl-7-iodo-1*H*-indazole, 1-acetyl-3-bromomethyl-7-fluoro-1*H*-indazole, 1-acetyl-3-bromomethyl-6,7-difluoro-1*H*-indazole, and 1-acetyl-3-bromomethyl-7-chloro-1*H*-indazole were similarly prepared from 3-chloroaniline, 2-iodoaniline, 2-fluoroaniline, 2,3-difluoroaniline and 2-chloroaniline, respectively.

Step E: 2-(1-Acetyl-6-fluoro-1*H*-indazol-3-ylmethyl)-1,2,3,4-tetrahydroisoquinoline

1-Acetyl-3-bromomethyl-6-fluoro-1*H*-indazole (0.53 g, 1.96 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was treated with 1,2,3,4-tetrahydroisoquinoline (0.261 g, 1.96 mmol) and Hünig's base (0.44 mL, 2.5 mmol) and the mixture stirred at 20°C for 16 h. The mixture was poured into saturated aqueous sodium bicarbonate solution (25 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 25 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), concentrated and the residue purified by flash chromatography (7% → 12% EtOAc in hexane) to give the title compound as a white solid (475 mg, 53%); mp 106–107°C (from Et<sub>2</sub>O / hexane); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO) δ 8.08 (dd, *J* = 8.8, 5.4 Hz, 1 H, indazole), 8.00 (dd, *J* = 9.6, 2.2 Hz, 1 H, indazole), 7.29 (dt, *J* = 9.1, 2.5 Hz, 1 H, indazole), 7.10 (m, 3 H, tetrahydroisoquinoline), 7.02 (m, 1 H, tetrahydroisoquinoline), 4.05 (s, 2 H, Ar-CH<sub>2</sub>N), 3.68 (s, 2 H, Ar-CH<sub>2</sub>N), 2.79 (m, 4 H,

tetrahydroisoquinoline) 2.72 (s, 3 H, Ac); MS (CI+) *m/e* 324 (M+H<sup>+</sup>); Anal. calcd for C<sub>19</sub>H<sub>18</sub>FN<sub>3</sub>O: C, 70.57; H, 5.61; N, 12.99. Found: C, 70.28; H, 5.32; N, 12.84.

5      Step F: 2-(6-Fluoro-1*H*-indazol-3-ylmethyl)-1,2,3,4-  
tetrahydroisoquinoline

2-(1-Acetyl-6-fluoro-1*H*-indazol-3-ylmethyl)-1,2,3,4-  
tetrahydroisoquinoline (300 mg, 0.93 mmol) in CH<sub>2</sub>Cl<sub>2</sub> / MeOH  
(1:1, 10 mL) was treated with sodium methoxide (2 mg) and  
stirred for 15 min at 20°C. The mixture was poured into  
10      saturated aqueous sodium bicarbonate solution (25 mL) and  
extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL). The combined organic  
extracts were dried (MgSO<sub>4</sub>), concentrated and purified by flash  
chromatography (50% EtOAc in hexane) to give the title  
compound as a colourless oil. Conversion to the hydrogen oxalate  
15      salt in MeOH / Et<sub>2</sub>O gave colourless crystals (202 mg, 59%); mp  
200–201 °C (from MeOH / Et<sub>2</sub>O); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO)  
δ 7.93 (dd, *J* = 8.8, 5.3 Hz, 1 H, indazole), 7.30 (dd, *J* = 9.7, 2.8  
Hz, 1 H, indazole), 7.15 – 6.97 (m, 5 H, aromatic), 4.25 (s, 2 H,  
Ar-CH<sub>2</sub>N), 3.88 (s, 2 H, Ar-CH<sub>2</sub>N), 3.00 (bs, 2 H,  
20      tetrahydroisoquinoline), 2.89 (bs, 2 H, tetrahydroisoquinoline);  
MS (CI+) *m/e* 282 (M+H<sup>+</sup>); Anal. calcd for C<sub>17</sub>H<sub>16</sub>FN<sub>3</sub>.  
(COOH)<sub>2</sub>. H<sub>2</sub>O: C, 65.35; H, 5.33; N, 12.71. Found: C, 65.40; H,  
5.24; N, 12.49.

EXAMPLE 5

25      2-(6-Chloro-1*H*-indazol-3-ylmethyl)-1,2,3,4-  
tetrahydroisoquinoline

The hydrogen oxalate salt of the title compound was  
prepared as a white crystalline solid following the general

procedure described in EXAMPLE 4; mp 212–214 °C (from EtOAc); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO) δ 13.3 (bs, 1 H, NH), 7.94 (d, *J* = 8.7 Hz, 1 H, indazole), 7.63 (s, 1 H, indazole), 7.18 – 7.09 (m, 5 H, aromatic), 4.36 (s, 2 H, Ar-CH<sub>2</sub>N), 3.98 (s, 2 H, Ar-CH<sub>2</sub>N), 3.10 (bs, 2 H, CH<sub>2</sub>N), 2.92 (bs, 2 H, CH<sub>2</sub>-Ar); MS (CI+) *m/e* 298 (M+H<sup>+</sup>); Anal. calcd for C<sub>17</sub>H<sub>16</sub>N<sub>3</sub>ClO<sub>4</sub>H<sub>2</sub>O: C, 57.51; H, 4.83; N, 10.58. Found: C, 57.74; H, 4.66; N, 10.32.

#### EXAMPLE 6

##### 10        2-(7-Chloro-1*H*-indazol-3-ylmethyl)-1,2,3,4-tetrahydroisoquinoline

The hydrogen oxalate salt of the title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 4; mp 122–124 °C (from EtOAc); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO) δ 7.92 (d, *J* = 7.9 Hz, 1 H, indazole), 7.49 (d, *J* = 6.9 Hz, 1 H, indazole), 7.20 – 7.08 (m, 5 H, aromatic), 4.44 (s, 2 H, Ar-CH<sub>2</sub>N), 4.05 (s, 2 H, Ar-CH<sub>2</sub>N), 3.17 (m, 2 H, CH<sub>2</sub>-N), 2.95 (m, 2 H, CH<sub>2</sub>-Ar); MS (CI+) *m/e* 297 (M+H<sup>+</sup>); Anal. calcd for C<sub>17</sub>H<sub>16</sub>N<sub>3</sub>Cl.C<sub>2</sub>O<sub>4</sub>H<sub>2</sub>. EtOAc: C, 57.80; H, 5.20; N, 9.63. Found: C, 57.41; H, 5.34; N, 9.83.

#### EXAMPLE 7

##### 7-Chloro-3-(4-phenethyl-3,6-dihydro-2*H*-pyridin-1-ylmethyl)-1*H*-indazole

The title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 4; mp 171–172°C (from EtOAc); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO) δ 13.31 (bs, 1 H, NH), 7.81 (d, *J* = 7.9 Hz, 1 H, indazole), 7.42 (d, *J*

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= 7.4 Hz, 1 H, indazole), 7.27 – 7.07 (m, 6 H, aromatic), 5.35 (s, 1 H, olefinic), 3.88 (s, 2 H, Ar-CH<sub>2</sub>N), 2.91 (s, 2 H, C=C-CH<sub>2</sub>-N), 2.66 (t, *J* = 7.7 Hz, 2 H, CH<sub>2</sub>), 2.55 (t, *J* = 5.6 Hz, 2 H, CH<sub>2</sub>-C-N), 2.20 (t, *J* = 7.7 Hz, 2 H, CH<sub>2</sub>), 2.04 (bs, 2 H, CH<sub>2</sub>-N); MS (CI+) *m/e* 352 (M+H<sup>+</sup>); Anal. calcd for C<sub>21</sub>H<sub>22</sub>N<sub>3</sub>Cl: C, 71.68; H, 6.30; N, 11.94. Found: C, 71.62; H, 6.07; N, 11.64.

#### EXAMPLE 8

##### 3-(4-(*E*)-Styryl-3,6-dihydro-2*H*-pyridin-1-ylmethyl)-1*H*-indazole

10           The title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 2; mp 207–209 °C (from EtOAc); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO) δ 12.83 (bs, 1 H, NH), 7.86 (d, *J* = 8.0 Hz, 1 H, indazole), 7.51 – 7.45 (m, 2 H, aromatic), 7.36 – 7.30 (m, 2 H, aromatic), 7.23 (m, 1 H, aromatic), 7.09 (m, 1 H, aromatic), 6.89 (d, *J* = 16.3 Hz, 1 H, CH=C), 6.47 (d, *J* = 16.3 Hz, 1 H, C=CH), 5.90 (bs, 1 H, olefinic), 3.94 (s, 2 H, Ar-CH<sub>2</sub>N), 3.14 (bs, 2 H, C=C-CH<sub>2</sub>-N), 2.67 (m, 2 H, CH<sub>2</sub>-C-N), 2.32 (bs, 2 H, CH<sub>2</sub>-N); MS (CI+) *m/e* 316 (M+H<sup>+</sup>); Anal. calcd for C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>·H<sub>2</sub>O: C, 76.16; H, 6.92; N, 12.69. Found: C, 76.26; H, 6.42; N, 12.40.

#### EXAMPLE 9

##### 7-Chloro-3-(4-(*E*)-styryl-3,6-dihydro-2*H*-pyridin-1-ylmethyl)-1*H*-indazole

25           The title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 4; mp 223–224 °C (from EtOAc); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO) δ 13.12 (bs, 1 H, NH), 7.82 (d, *J* = 7.8 Hz, 1 H, indazole), 7.43 –

7.37 (m, 3 H, aromatic), 7.29 (m, 2 H, aromatic), 7.18 (m, 1 H, aromatic), 7.08 (m, 1 H, aromatic), 6.82 (d,  $J = 16.4$  Hz, 1 H, CH=C), 6.46 (d,  $J = 16.4$  Hz, 1 H, C=CH), 5.87 (bs, 1 H, olefinic), 3.96 (s, 2 H, Ar-CH<sub>2</sub>N), 3.16 (bs, 2 H, C=C-CH<sub>2</sub>-N), 2.69 (m, 2 H, CH<sub>2</sub>-C-N), 2.32 (bs, 2 H, CH<sub>2</sub>-N); MS (CI+)  $m/e$  350 (M+H<sup>+</sup>); Anal. calcd for C<sub>21</sub>H<sub>20</sub>N<sub>3</sub>Cl: C, 72.09; H, 5.76; N, 12.01. Found: C, 72.14; H, 5.85; N, 11.99.

#### EXAMPLE 10

##### 10 3-(4-Naphthalen-2-yl-3,6-dihydro-2H-pyridin-1-ylmethyl)-1H-indazole

The title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 2; mp 225–227 °C (from EtOAc); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO)  $\delta$  12.83 (bs, 1 H, NH), 7.90 – 7.83 (m, 5 H, aromatic), 7.67 (m, 1 H, aromatic), 7.51 – 7.43 (m, 3 H, aromatic), 7.33 (t,  $J = 7.1$  Hz, 1 H, indazole), 7.09 (t,  $J = 7.6$  Hz, 1 H, indazole), 6.35 (bs, 1 H, olefinic), 3.98 (s, 2 H, Ar-CH<sub>2</sub>N), 3.21 (m, 2 H, C=C-CH<sub>2</sub>-N), 2.77 (m, 2 H, CH<sub>2</sub>-C-N), 2.60 (bs, 2 H, CH<sub>2</sub>-N); MS (CI+)  $m/e$  340 (M+H<sup>+</sup>); Anal. calcd for C<sub>23</sub>H<sub>21</sub>N<sub>3</sub>O: C, 79.28; H, 6.36; N, 12.06. Found: C, 79.65; H, 6.22; N, 11.80.

#### EXAMPLE 11

##### 7-Chloro-3-[4-(4-chlorophenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole

The title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 4; mp 171–173°C (from EtOAc); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO)  $\delta$  13.37 (bs, 1 H, NH), 7.85 (d,  $J = 8.0$  Hz, 1 H, indazole), 7.43 (d,  $J$



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= 8.6 Hz, 3 H, 2 x Ph, 1 x indazole), 7.36 (d,  $J$  = 8.6 Hz, 2 H, Ph), 7.10 (t,  $J$  = 7.7 Hz, 1 H, indazole), 6.19 (bs, 1 H, olefinic), 3.96 (s, 2 H, Ar-CH<sub>2</sub>N), 3.15 (m, 2 H, C=C-CH<sub>2</sub>-N), 2.70 (t,  $J$  = 5.6 Hz, 2 H, CH<sub>2</sub>-C-N), 2.44 (bs, 2 H, CH<sub>2</sub>-N); MS (CI+)  $m/e$  358 (M+H<sup>+</sup>);  
5 Anal. calcd for C<sub>19</sub>H<sub>17</sub>N<sub>3</sub>Cl<sub>2</sub>O H<sub>2</sub>O: C, 62.91; H, 4.86; N, 11.58.  
Found: C, 63.22; H, 4.66; N, 11.48.

### EXAMPLE 12

#### 3-[4-(4-Methoxyphenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole

10 The title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 2; mp 157–159°C (from EtOAc); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO)  $\delta$  12.81 (bs, 1 H, NH), 7.85 (d,  $J$  = 8.1 Hz, 1 H, indazole), 7.48 (d,  $J$  = 8.4 Hz, 1 H, indazole), 7.48 (d,  $J$  = 8.4 Hz, 2 H, Ph), 7.47 (t,  $J$  = 8.4 Hz, 1 H, indazole), 7.08 (t,  $J$  = 7.8 Hz, 1 H, indazole), 6.87 (d,  $J$  = 8.9 Hz, 2 H, Ph), 6.02 (bs, 1 H, olefinic), 3.93 (s, 2 H, Ar-CH<sub>2</sub>N), 3.73 (s, 3 H, OMe), 3.13 (m, 2 H, C=C-CH<sub>2</sub>-N), 2.69 (m, 2 H, CH<sub>2</sub>-C-N), 2.42 (bs, 2 H, CH<sub>2</sub>-N); MS (CI+)  $m/e$  320 (M+H<sup>+</sup>); Anal. calcd for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O<sub>0</sub> H<sub>2</sub>O: C, 73.15; H, 6.75; N, 12.80. Found: C, 73.58; H, 6.45; N, 12.61.  
20

### EXAMPLE 13

#### 7-Chloro-3-[4-(4-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole

25 The title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 4; mp 201–203°C (from EtOAc); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO)  $\delta$  13.36 (bs, 1 H, NH), 7.85 (d,  $J$  = 8.0 Hz, 1 H, indazole), 7.43 (d,  $J$

= 7.4 Hz, 1 H, indazole), 7.33 (d,  $J$  = 8.8 Hz, 2 H, Ph), 7.10 (t,  $J$  = 7.8 Hz, 1 H, indazole), 6.87 (d,  $J$  = 8.8 Hz, 2 H, Ph), 6.02 (bs, 1 H, olefinic), 3.95 (s, 2 H, Ar-CH<sub>2</sub>N), 3.74 (s, 3 H, OMe), 3.12 (m, 2 H, C=C-CH<sub>2</sub>N), 2.69 (t,  $J$  = 5.6 Hz, 2 H, CH<sub>2</sub>-C-N), 2.42 (bs, 2 H, CH<sub>2</sub>-N); MS (CI+)  $m/e$  354 (M+H<sup>+</sup>); Anal. calcd for C<sub>20</sub>H<sub>20</sub>N<sub>3</sub>ClO: C, 67.89; H, 5.70; N, 11.88. Found: C, 68.02; H, 5.59; N, 11.61.

#### EXAMPLE 14

##### 10 7-Fluoro-3-[4-(4-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole

The title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 4; mp 183–185°C (from EtOAc); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO)  $\delta$  13.39 (bs, 1 H, NH), 7.69 (d,  $J$  = 8.0 Hz, 1 H, indazole), 7.34 (d,  $J$  = 8.7 Hz, 2 H, Ph), 7.18 (m, 1 H, indazole), 7.06 (m, 1 H, indazole), 6.87 (d,  $J$  = 8.7 Hz, 2 H, Ph), 6.02 (bs, 1 H, olefinic), 3.95 (Ar-CH<sub>2</sub>-N), 3.73 (s, 3 H, OMe), 3.12 (bs, 2 H, C=C-CH<sub>2</sub>-N), 2.69 (t,  $J$  = 5.4 Hz, 2 H, CH<sub>2</sub>-C-N), 2.42 (bs, 2 H, CH<sub>2</sub>-N); MS (CI+)  $m/e$  338 (M+H<sup>+</sup>); Anal. calcd for C<sub>20</sub>H<sub>20</sub>FN<sub>3</sub>O + H<sub>2</sub>O: C, 70.26; H, 6.04; N, 12.29. Found: C, 70.35; H, 5.54; N, 12.37.

#### EXAMPLE 15

##### 6,7-Difluoro-3-[4-(4-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole

The title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 4; mp 195–197°C (from EtOAc); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO)  $\delta$  13.54 (bs, 1 H, NH), 7.70 (dd,  $J$  = 8.8, 4.2 Hz, 1 H, indazole), 7.34

(d,  $J = 8.8$  Hz, 2 H, Ph), 7.14 (dd,  $J = 17.6, 8.8$  Hz, 1 H, indazole), 6.87 (d,  $J = 8.8$  Hz, 2 H, Ph), 6.02 (bs, 1 H, olefinic), 3.94 (bs, Ar-CH<sub>2</sub>N), 3.73 (s, 3 H, OMe), 3.12 (m, 2 H, C=C-CH<sub>2</sub>-N), 2.68 (t,  $J = 5.6$  Hz, 2 H, CH<sub>2</sub>-C-N), 2.42 (bs, 2 H, CH<sub>2</sub>-N); MS (CI+)  $m/e$  356 (M+H<sup>+</sup>); Anal. calcd for C<sub>20</sub>H<sub>19</sub>N<sub>3</sub>F<sub>2</sub>O<sub>0</sub> H<sub>2</sub>O: C, 66.47; H, 5.49; N, 11.63. Found: C, 66.35; H, 5.23; N, 11.51.

#### EXAMPLE 16

##### 3-(4-Benzofuran-5-yl-3,6-dihydro-2H-pyridin-1-ylmethyl)-1H-indazole

10 The title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 4; mp 193–194°C (from EtOAc); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO)  $\delta$  12.83 (bs, 1 H, NH), 7.95 (bs, 1 H, benzofuran), 7.87 (d,  $J = 7.6$  Hz, 1 H, indazole), 7.64 (s, 1 H, benzofuran), 7.50 (m, 2 H, benzofuran, indazole), 7.40 – 7.31 (m, 2 H, benzofuran, indazole), 7.09 (t,  $J = 7.5$  Hz, 1 H, indazole), 6.91 (bs, 1 H, benzofuran), 6.12 (bs, 1 H, olefinic), 3.96 (s, 2 H, Ar-CH<sub>2</sub>-N), 3.16 (bs, 2 H, C=C-CH<sub>2</sub>-N), 2.73 (bs, CH<sub>2</sub>-C-N), 2.50 (bs, 2 H, CH<sub>2</sub>-N); MS (CI+)  $m/e$  330 (M+H<sup>+</sup>); Anal. calcd for C<sub>21</sub>H<sub>19</sub>N<sub>3</sub>O: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.28; H, 5.64; N, 12.59.

#### EXAMPLE 17

##### 3-(4-Benzofuran-5-yl-3,6-dihydro-2H-pyridin-1-ylmethyl)-7-chloro-1H-indazole

25 The title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 2; mp 218–222°C (from EtOAc); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO)  $\delta$  13.36 (bs, 1 H, NH), 7.95 (bs, 1 H, benzofuran), 7.87 (d,  $J = 7.6$

Hz, 1 H, indazole), 7.64 (bs, 1 H, benzofuran), 7.51 (d,  $J = 8.5$  Hz, 1 H, benzofuran), 7.41 (m, 2 H, benzofuran, indazole), 7.11 (m, 1 H, indazole), 6.91 (bs, 1 H, benzofuran), 6.12 (bs, 1 H, olefinic), 3.98 (s, 2 H, Ar-CH<sub>2</sub>N), 3.16 (bs, 2 H, C=C-CH<sub>2</sub>-N), 2.73 (bs, 2 H, CH<sub>2</sub>-C-N), 2.50 (bs, 2 H, CH<sub>2</sub>-N); MS (CI+)  $m/e$  (M+H<sup>+</sup>); Anal. calcd for C<sub>21</sub>H<sub>18</sub>N<sub>3</sub>OCl: C, 69.32; H, 4.99; N, 11.55. Found: C, 69.23; H, 4.78; N, 11.31.

### EXAMPLE 18

10 3-(4-Benzofuran-5-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl)-1H-indazole

The title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 2; mp 139–141°C (from EtOAc); <sup>1</sup>H NMR (360 MHz, d<sub>6</sub>-DMSO)  $\delta$  12.82 (bs, 1 H, NH), 7.85 (d,  $J = 8.1$  Hz, 1 H, indazole), 7.48 (d,  $J = 8.4$  Hz, 1 H, indazole), 7.33 (t,  $J = 7.2$  Hz, 1 H, indazole), 7.08 (t,  $J = 7.4$  Hz, 1 H, indazole), 7.01 (s, 1 H, Ph), 6.85 (m, 2 H, Ph), 6.03 (bs, 1 H, olefinic), 5.98 (s, 2 H, O-CH<sub>2</sub>-O), 3.93 (s, 2 H, Ar-CH<sub>2</sub>N), 3.11 (m, 2 H, C=C-CH<sub>2</sub>-N), 2.68 (t,  $J = 5.6$  Hz, 2 H, CH<sub>2</sub>-C-N), 2.40 (bs, 2 H, CH<sub>2</sub>-N); MS (CI+)  $m/e$  334.52 (M+H<sup>+</sup>); Anal. calcd for C<sub>20</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub> H<sub>2</sub>O: C, 71.09; H, 5.82; N, 12.44. Found: C, 71.15; H, 5.71; N, 12.22.

### EXAMPLE 19

25 3-[4-(1H-Indol-5-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole

The hydrogen oxalate salt of the title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 2; mp 198–200°C (from MeOH

/ EtOAc);  $^1\text{H}$  NMR (360 MHz,  $\text{d}_6$ -DMSO)  $\delta$  13.35 (bs, 1 H, NH), 11.10 (bs, 1 H, NH), 7.97 (d,  $J = 8.1$  Hz, 1 H, indazole), 7.59 (bs, 2 H, indole, indazole), 7.41 (t,  $J = 7.3$  Hz, 1 H, indazole), 7.33 (m, 2 H, indole), 7.21 (m, 2 H, indole, indazole), 6.42 (bs, 1 H, indole), 6.08 (bs, 1 H, olefinic), 4.58 (bs, 1 H, Ar-CH<sub>2</sub>-N), 3.74 (bs, 1 H, Ar-CH<sub>2</sub>-N), 3.32 (bs, 4 H, 2 x CH<sub>2</sub>), 2.76 (bs, 2 H, CH<sub>2</sub>); MS (CI+)  $m/e$  329 (M+H<sup>+</sup>); Anal. calcd for C<sub>21</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>H<sub>2</sub>: C, 66.02; H, 5.29; N, 13.39. Found: C, 65.93; H, 5.19; N, 12.64.

#### EXAMPLE 20

##### 10        7-Chloro-3-[4-(1H-indol-5-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole

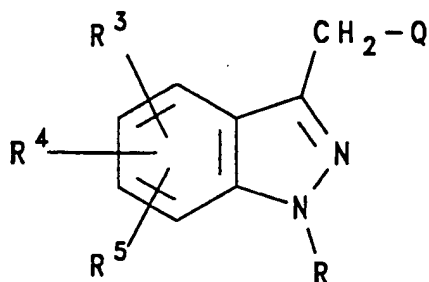
The title compound was prepared as a white crystalline solid following the general procedure described in EXAMPLE 4; mp 164–167°C (from EtOAc);  $^1\text{H}$  NMR (360 MHz,  $\text{d}_6$ -DMSO)  $\delta$  13.36 (bs, 1 H, NH), 11.01 (bs, 1 H, NH), 7.87 (d,  $J = 8.0$  Hz, 1 H, indazole), 7.53 (s, 1 H, indole), 7.43 (d,  $J = 7.4$  Hz, 1 H, indazole), 7.30 (m, 2 H, indole), 7.20 (m, 1 H, indole), 7.11 (t,  $J = 7.8$  Hz, 1 H, indazole), 6.38 (bs, 1 H, indazole), 6.03 (bs, 1 H, olefinic), 3.97 (s, 2 H, Ar-CH<sub>2</sub>-N), 3.15 (bs, 2 H, C=C-CH<sub>2</sub>-N), 2.72 (m, 2 H, CH<sub>2</sub>-C-N), 2.50 (bs, 2 H, CH<sub>2</sub>-N); MS (CI+)  $m/e$  363 (M+H<sup>+</sup>); Anal. calcd for C<sub>21</sub>H<sub>19</sub>N<sub>4</sub>ClO H<sub>2</sub>O: C, 67.02; H, 5.49; N, 14.89. Found: C, 66.88; H, 5.16; N, 14.64.

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CLAIMS:

1. A compound of formula I, or a salt or prodrug thereof:

5

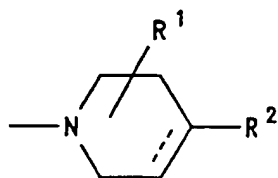


( I )

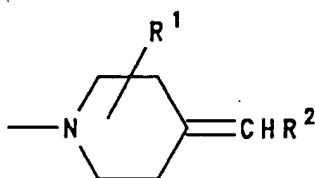
15 wherein

R represents hydrogen or C<sub>1-6</sub> alkyl;

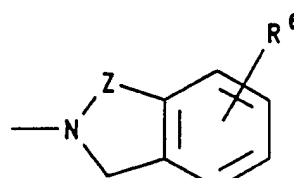
Q represents a moiety of formula Qa, Qb or Qc:



( Q a )



( Q b )



( Q c )

in which the broken line represents an optional chemical bond;

30 R<sup>1</sup> represents hydrogen, or an optionally substituted C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl(C<sub>1-6</sub>)alkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, aryl(C<sub>1-6</sub>)alkoxy, aryl(C<sub>2-6</sub>)alkenyl, aryl(C<sub>2-6</sub>)alkynyl, heteroaryl, heteroaryl(C<sub>1-6</sub>)alkyl, heteroaryl(C<sub>2-6</sub>)alkenyl or heteroaryl(C<sub>2-6</sub>)alkynyl group;

35 R<sup>2</sup> represents an optionally substituted C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub>

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cycloalkyl, C<sub>3-7</sub> cycloalkyl(C<sub>1-6</sub>)alkyl, aryl,  
 aryl(C<sub>1-6</sub>)alkyl, aryl(C<sub>1-6</sub>)alkoxy, aryl(C<sub>2-6</sub>)alkenyl,  
 aryl(C<sub>2-6</sub>)alkynyl, heteroaryl, heteroaryl(C<sub>1-6</sub>)alkyl,  
 heteroaryl(C<sub>2-6</sub>)alkenyl or heteroaryl(C<sub>2-6</sub>)alkynyl group;

5           R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen,  
 hydrocarbon, a heterocyclic group, halogen, cyano,  
 trifluoromethyl, nitro, -OR<sup>a</sup>, -SR<sup>a</sup>, -SOR<sup>a</sup>, -SO<sub>2</sub>R<sup>a</sup>,  
 -SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>R<sup>b</sup>, -NR<sup>a</sup>COR<sup>b</sup>, -NR<sup>a</sup>CO<sub>2</sub>R<sup>b</sup>, -COR<sup>a</sup>, -CO<sub>2</sub>R<sup>a</sup> or  
 -CONR<sup>a</sup>R<sup>b</sup>;

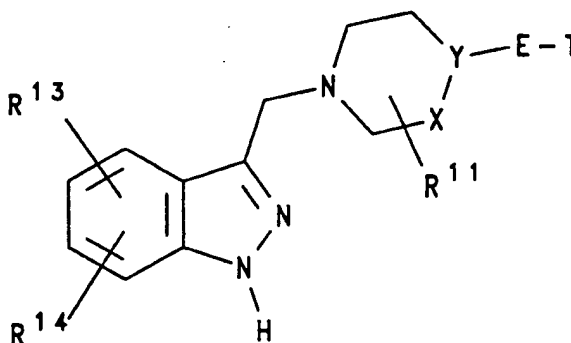
10           Z represents -CH<sub>2</sub>- or -CH<sub>2</sub>CH<sub>2</sub>-;

R<sup>6</sup> represents hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub>  
 alkoxy, aryl(C<sub>1-6</sub>)alkyl or halogen; and

R<sup>a</sup> and R<sup>b</sup> independently represent hydrogen,  
 hydrocarbon or a heterocyclic group.

15

2. A compound as claimed in claim 1  
 represented by formula IIA, and salts and prodrugs  
 thereof:



( I I A )

wherein

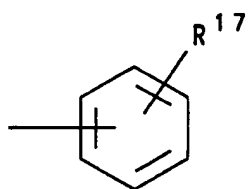
30           E represents -(CH<sub>2</sub>)<sub>n</sub>-, -CH=CH- or -C≡C-;  
 n is zero, 1, 2 or 3;

-X-Y- represents -CH<sub>2</sub>-CH- or -CH=C-;

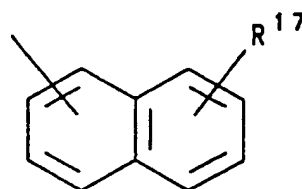
T represents a group of formula (i), (ii),  
 (iii) or (iv):

35

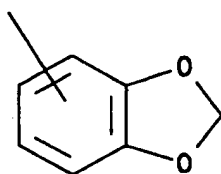
- 38 -



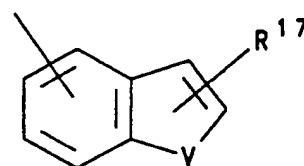
(I)



(II)



(III)



(IV)

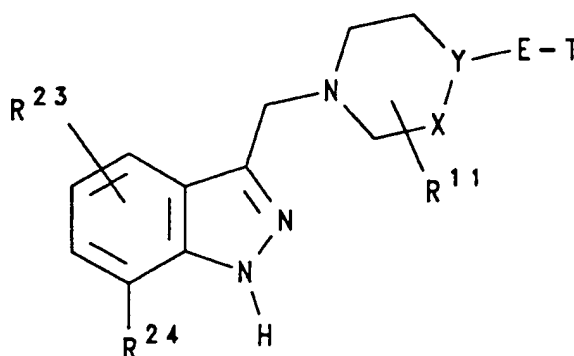
in which V represents oxygen, sulphur or NH;

$R^{11}$  represents hydrogen or  $C_{1-6}$  alkyl; and

$R^{13}$ ,  $R^{14}$  and  $R^{17}$  independently represent

20 hydrogen, halogen, cyano, nitro, trifluoromethyl, amino,  
 $C_{1-6}$  alkylamino, di( $C_{1-6}$ )alkylamino,  $C_{1-6}$  alkyl,  $C_{1-6}$   
 alkoxy, aryl( $C_{1-6}$ )alkoxy or  $C_{2-6}$  alkylcarbonyl.

3. A compound as claimed in claim 2  
 25 represented by formula IIB, and salts and prodrugs  
 thereof:



(IIB)



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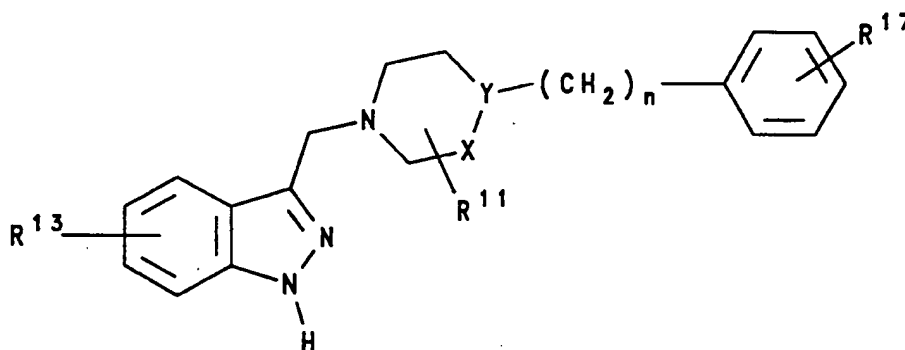
wherein

X, Y, R<sup>11</sup>, E and T are as defined in claim 2;

and

R<sup>23</sup> and R<sup>24</sup> independently represent hydrogen,  
 5 halogen, cyano, nitro, trifluoromethyl, amino, C<sub>1-6</sub>  
 alkylamino, di(C<sub>1-6</sub>)alkylamino, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy,  
 aryl(C<sub>1-6</sub>)alkoxy or C<sub>2-6</sub> alkylcarbonyl.

4. A compound as claimed in claim 2  
 10 represented by formula IIC, and salts and prodrugs  
 thereof:



(IIC)

wherein n, X, Y, R<sup>11</sup>, R<sup>13</sup> and R<sup>17</sup> are as defined in claim  
 2.

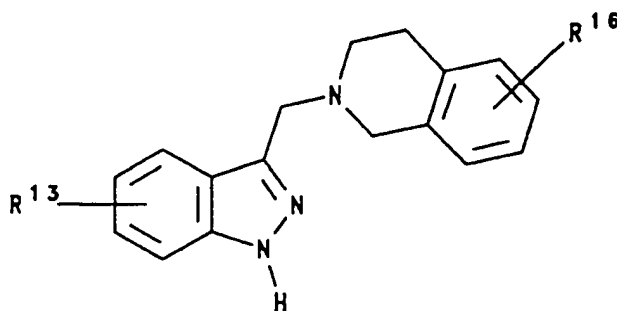
25

5. A compound as claimed in claim 1  
 represented by formula IID, and salts and prodrugs  
 thereof:

30

35

- 40 -



(11D)

wherein

R<sup>13</sup> is as defined in claim 2; and

R<sup>16</sup> represents hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, aryl(C<sub>1-6</sub>)alkyl or halogen.

15

6. A compound as claimed in claim 1 selected from:

3-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-1H-indazole;

3-[4-(2-phenylethyl)piperidin-1-ylmethyl]-1H-indazole;

20 3-[4-(2-cyclohexylethyl)piperidin-1-ylmethyl]-1H-indazole;

6-fluoro-3-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-1H-indazole;

25 7-chloro-3-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-1H-indazole;

6-chloro-3-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-1H-indazole;

7-chloro-3-[4-(2-phenylethyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;

30 (E)-3-[4-(2-phenylethenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;

7-chloro-(E)-3-[4-(2-phenylethenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;

35 3-[4-(naphthalen-2-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;

- 41 -

- 7-chloro-3-[4-(4-chlorophenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
3-[4-(4-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
5 7-chloro-3-[4-(4-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
7-fluoro-3-[4-(4-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
6,7-difluoro-3-[4-(4-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
10 3-[4-(benzofuran-5-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
3-[4-(benzofuran-5-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-7-chloro-1H-indazole;  
15 3-[4-(benzo[1,3]dioxolan-5-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
3-[4-(1H-indol-5-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
7-chloro-3-[4-(1H-indol-5-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-1H-indazole;  
20 and salts and prodrugs thereof.

7. A pharmaceutical composition comprising a compound as claimed in any one of the preceding claims in association with a pharmaceutically acceptable carrier.  
25

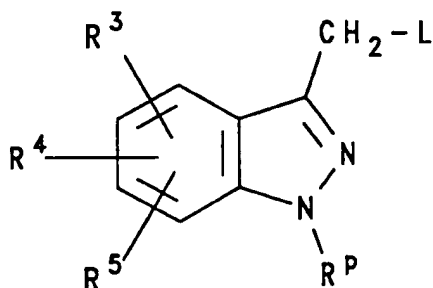
8. A compound as claimed in any one of claims 1 to 6 for use in therapy.

9. The use of a compound as claimed in any one of claims 1 to 6 for the manufacture of a medicament for the treatment and/or prevention of disorders of the dopamine system.  
30

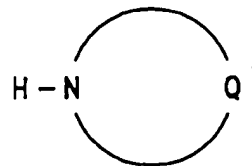
10. A process for the preparation of a compound as claimed in claim 1, which comprises:  
35

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(A) reacting a compound of formula III with a compound of formula IV:



(III)

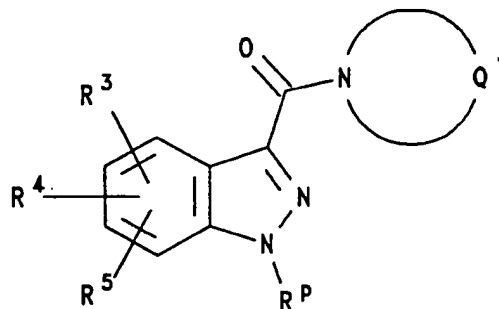


(IV)

15 wherein  $R^3$ ,  $R^4$  and  $R^5$  are as defined in claim 1,  $Q^1$  represents the residue of a moiety of formula Qa to Qc as defined in claim 1, L represents a suitable leaving group, and  $R^P$  corresponds to the group R as defined in claim 1 or represents a suitable protecting group;  
 20 followed, where required, by removal of the protecting group  $R^P$ ; and subsequently, if necessary, N-alkylation by standard methods to introduce the moiety R; or

(B) reducing a compound of formula V:

25



(V)

35 wherein  $R^3$ ,  $R^4$  and  $R^5$  are as defined in claim 1, and  $Q^1$  and  $R^P$  are as defined above; followed, where required, by

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removal of the protecting group  $R^P$ ; and subsequently, if necessary, N-alkylation by standard methods to introduce the moiety R; and

- 5                   (C) subsequently, where required, converting a compound of formula I initially obtained into a further compound of formula I by conventional methods.

- 10                   11. A method for the treatment and/or prevention of disorders of the dopamine system, which method comprises administering to a patient in need of such treatment an effective amount of a compound as claimed in any one of claims 1 to 6.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 94/00503

## A. CLASSIFICATION OF SUBJECT MATTER

IPC : C07D 401/06, C07D 403/06, C07D 405/14, A61K 31/415, A61K 31/435  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC : C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 3678059 (HEINZ WERNER GSCHWEND ET AL), 18 July 1972 (18.07.72), see the whole document ---	1-10
A	US, A, 3488353 (SYDNEY ARCHER), 6 January 1970 (06.01.70), see the whole document --	1-10
A	EP, A1, 0518805 (H. LUNDBECK A/S), 16 December 1992 (16.12.92), page 24, line 50 --	1-10

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\* Special categories of cited documents

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\*Z\* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

9 June 1994

- 4. 07. 94

Name and mailing address of the international Searching Authority

Authorized officer



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Göran Karlsson

2

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 94/00503

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EP, A2, 0449186 (THE DU PONT MERCK PHARMACEUTICAL COMPANY), 2 October 1991 (02.10.91), page 1 - page 5</p> <p style="text-align: center;">-- -----</p>	1-10

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 94/00503

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11  
because they relate to subject matter not required to be searched by this Authority, namely:  
A method for treatment of the human or animal body by  
therapy, see Rule 39.1.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such  
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.



**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

07/05/94

International application No.  
PCT/GB 94/00503

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US-A-	3678059	18/07/72	NONE		
US-A-	3488353	06/01/70	NONE		
EP-A1-	0518805	16/12/92	AU-A-	1984892	12/01/93
			EP-A-	0593511	27/04/94
			FI-D-	935558	00/00/00
			WO-A-	9222554	23/12/92
EP-A2-	0449186	02/10/91	JP-A-	4364164	16/12/92
			US-A-	5116846	26/05/92